REMARKS

Amendments

Claims 1, 3, 5, 7, 8 and 9 have been amended to recite that the claimed polypeptides "specifically bind to an anti-*Ehrlichia* antibody." Support for the amendments can be found, *inter alia*, at page 9, lines 8-15. Claim 2 inadvertently depended from itself, so it has been amended to properly depend from claim 1. Claims 3, 5, 8 and 9 have been amended to recite polypeptides "consisting essentially of" the polypeptides of SEQ ID NO:2 or variants thereof.

All amendments are made without prejudice, and the Applicants reserve the right to pursue the subject matter in a continuation application. No new matter is added by these amendments, and Applicants respectfully request their entry.

The Applicants wish to thank the Examiner for withdrawing the objections to the specification and claims as outlined in the Office Action of July 3, 2002. The Applicants also wish to thank the Examiner for withdrawing the rejection of claim 1-6 under 35 U.S.C. § 102(b) as related to the reference by Zhi *et al.*

Rejection of Claims 1-9 Under 35 U.S.C. §112, first paragraph

Claims 1-9 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking written description. Applicants respectfully traverse the rejection.

The claims recite, *inter alia*, compositions of matter and articles of manufacture consisting essentially of an isolated polypeptide shown in SEQ ID NO:2, a phenotypically silent amino acid substitution variant thereof, or a conservative amino acid substitution variant thereof, that specifically binds to an anti-*Ehrlichia* antibody.

The Office Action asserts that the genus of claimed polypeptides is highly variant. The claimed genus, however, is not as highly variant as the Office asserts. The claims recite

polypeptides that consist essentially of SEQ ID NO:2 and specified variants thereof. SEQ ID NO:2 is about 20 amino acids long. The specification teaches that:

> the invention provides polypeptides having at least 85% identity, more preferably at least 90% identity, and still more preferably at least 96%, 97%, 98%, or 99% identity to a polypeptide sequence shown in SEQ ID NOs:1-7. See specification, page 5, second full paragraph.

Therefore, in an about 20 amino acid polypeptide only about 3 substitutions are allowed to retain at least 85% identity with SEQ ID NO:2. As such, the genus is not as highly variant as the Office asserts. It is routine in the art, given the extensive teaching in the specification of what constitutes a "variant" to design and screen a variant polypeptide of SEQ ID NO:2 for up to about 3 amino acid substitutions (see, e.g., Specification, page 5, lines 7-14; page 7, line 12 through page 9, line 7, *citing* Bowie *et al.*, Science, 247: 1306 (1990)(copy attached), which teaches methods of construction of variants and the tolerance of protein sequences of substitutions); page 18, line 19 through page 19, line 13; page 7, line 6 through page 9, line 7 (teaching and how to make and screen the variants); page 8, lines 9-20 (teaching that proteins are surprisingly tolerant of amino acid substitutions and providing guidance to the types of amino acid substitutions that are well tolerated)).

The Office Action further asserts that the Applicants have provided no structural description accompanying the variant language recited in the claims. The written description requirement, however, does not require a structural description. Rather:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

> Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶1, "Written Description" Requirement, 66 Fed. Reg. 1099, 1106 (2001) (citations omitted).

Clearly, there is no absolute requirement for a structural description under the Written Description requirement. Instead, the disclosure is considered as a whole in determining whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, the applicant was in possession of the claimed invention. *See id.* at 1105.

Nonetheless, the Applicants respectfully disagree with the Office's assertion that no structural description is provided in the instant application. The specification recites that the variants of the invention comprise at least 85% identity to, in this case, SEQ ID NO:2. Since SEQ ID NO:2 is about 20 amino acids long, about three amino acid substitutions are allowed according to the specification. By definition, a very significant amount of structural description and a significantly detailed chemical structure is provided by way of the 85% or more of the sequence described by SEQ ID NO:2 that is unperturbed in the variants. The specification teaches the kinds of substitutions that are considered conservative (e.g., page 7, line 6 through page 9, line 7), and clearly demonstrates that Applicants possessed conservative amino acid substitution variants of SEQ ID NO:2. Further, combined with the teaching in the specification, and in Bowie *et al.* that proteins are surprisingly tolerant to substitutions in general, the specification clearly demonstrates that Applicants had possession of phenotypically silent variants (*e.g.* page 8, lines 3-20 and Bowie *et al.*).

The Office Action also asserts that it is not routine in the art to screen for multiple substitutions, that the positions within the polypeptide's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in any polypeptide, and that the result of such modifications is unpredictable based on

the instant disclosure. However, it appears that the Office has failed to consider the large body of art pertaining to amino acid substitutions. See, for example, Johnson *et al.,* Journal of Molecular Biology. 233: 716-738 (1993); Karlin *et al.,* Proc. Natl. Acad. Sci. USA. 87: 2264-2268 (1990); and Altschul, Journal of Molecular Biology, 219: 555-665 (1991); attached hereto. These references provide evidence of the detailed information available to one of skill in the art regarding the substitution of amino acids in a polypeptide with a reasonable expectation of success. For example, Bowie teaches "[a]n amino acid sequence encodes a message that determines the shape and function of a protein. This message is highly degenerate in that many different sequences can code for proteins with essentially the same structure and activity." Bowie *et al.* p. 1306. Johnson, Karlin and Altchul demonstrate methods of aligning protein sequences. Such alignments can provide insight into which amino acids of a polypeptide can be substituted by alignment with other similar polypeptides.

Moreover, sensitivity to substitutions is in large part based on upset of the packing of tertiary and quaternary structure present in most full size proteins. See, e.g., Bowie, page 1307. Branden & Tooze, Introduction to Protein Structure, Garland Publishing 1991 (copy of pages 12, 15 are attached) teach that the average length of helix is 10 amino acids, and a single strand of beta sheet is 7 amino acids. Thus, one of skill in the art would expect that tertiary structure is minimal in short sequences. This is especially relevant for the about 20 amino acid sequences of the invention, because tertiary structure is minimal to nonexistent and quaternary structure is nonexistent. Consequently, concerns about disruption of function by amino acid substitution, for example, through disruption of amino acid packing at the core of a folded protein are minimized for the about 20 amino acid polypeptides of the invention.

Still further, those of skill in the art would know that, as Bowie observed in 1990, "An amino acid sequence encodes a message that determines the shape and function of a protein. This message is highly degenerate in that many different sequences can code for proteins with essentially the same structure and activity." Bowie *et al.* p. 1306. Thus, contrary to the assertions of the Office, the practitioner would expect that substitutions could be made to the polypeptide sequence with a reasonable expectation of success, i.e., that the resulting sequence binds to anti-*Ehrlichia* antibodies.

Furthermore, making and testing the polypeptides and variants of the invention are trivial as outlined in the specification at, *inter alia*, page 10, line 6 through page 11, line 6; page 11, line 21 through page 16, line 8; Example 1, page 17, line 11 through page 19, line 13. Thus, it is trivial and routine to screen for possible substitutions while maintaining 85% or greater identity and maintaining binding to anti-*Ehrlichia* antibodies according to the specification and there is a reasonable expectation of success in so doing. Consequently, one of skill in the art would know that the specification provides sufficient disclosure allowing her to clearly recognize that the Applicants invented what is claimed. See *in re Gostelli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989).

Given the teaching of the specification and the prior art, it is clear that Applicants were in possession of polypeptides consisting essentially of the about 20 amino acid polypeptide of SEQ ID NO:2 or phenotypically silent or conservative amino acid substitution variants of SEQ ID NO:2 that specifically bind to an anti-*Ehrlichia* antibody. Thus, the specification fulfills the written description requirement of 35 U.S.C. § 112, first paragraph. Accordingly, Applicants respectfully request withdrawal of the rejection.

Rejection of Claims 1-9 Under 35 U.S.C. §112, first paragraph

Claims 1-9 stand rejected under 35 U.S.C. §112, first paragraph as allegedly lacking enablement. Applicants respectfully traverse the rejection.

The Office Action asserts that the specification does not provide enablement for a composition or an article of manufacture that comprise variants of SEQ ID NO:2. Under 35 U.S.C. § 112, all that is required is that the specification describe the invention in such terms as to enable a person skilled in the art to make and use the invention. Specifically, The test of enablement is whether one reasonably skilled in the art (1) could make and use the invention (2) from the disclosures in the patent coupled with information known in the art (3) without undue experimentation. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988); *United States v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); M.P.E.P. § 2164.01. "The determination of what constitutes undue experimentation is a given case requires the application of a standard of reasonableness, having due regard of the nature of the invention and the state of the art." *In re Wa*nds, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988) (citing *Ansul Co. v. Uniroyal, Inc.*, 169 U.S.P.Q. 759, 762-63 (2d Cir. 1971). "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Id.* Thus, in the instant case, the specification must teach one skilled in the art how to make and use polypeptides consisting essentially of the about 20 amino acid polypeptide of SEQ ID NO:2 or phenotypically silent or conservative amino acid substitution variants of SEQ ID NO:2 that specifically bind to an anti-*Ehrlichia* antibody.

Initially, the specification provides ample guidance for one to make and use the invention. For example, the specification provides extensive teaching regarding making and

screening or using the polypeptides of the invention (see e.g., page 7, line 14 through page 10, line 13 (making) and, e.g., page 11, line 21 through page 16, line 8; Example 1; and page 9, line 8 through page 10, line 5; page 11, line 21 through page 21, line 16 (using/screening).

The Office alleges that "Applicant has provided no structural description accompanying the variant language recited in the claims." (see page 7 of 1/24/03 Office action; emphasis in the original). However, a structural description is not required for enablement. Rather, one of skill in the art must be able to make and use the invention, given the specification coupled with information known in the art, without undue experimentation.

Nonetheless, the instant specification provides ample structural description of the claimed polypeptides. The specification, for example, teaches that variants of the invention comprise at least 85% identity to, in this case, SEQ ID NO:2. Therefore, about three substitutions of SEQ ID NO:2 are allowed according to the specification. By definition, a very significant amount of structural description and a significantly detailed chemical structure is provided by way of the 85% or more of the sequence described by SEQ ID NO:2 that is unperturbed in the variants. Combined with the knowledge of one of skill in the art pertaining to the kinds of substitutions that are considered conservative (*see, e.g.* Discussion of Johnson *et al.,* Karlin *et al.,* and Altschul, *supra*), and the teaching in the specification (e.g., page 7, line 6 through page 9, line 7), the practitioner is provided with full enablement to make and use the conservative substitution variants as claimed. Further, combined with the teaching in the specification, and in Bowie *et al.*, that proteins are quite tolerant to substitutions and the knowledge that producing polypeptides of lengths contemplated in the invention is routine, the practitioner is provided with full enablement to make and use the phenotypically silent variants as claimed.

The Office Action asserts that it is not routine in the art to screen for multiple substitutions, that the positions within the polypeptide's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in any polypeptide, and that the result of such modifications is unpredictable based on the instant disclosure. This assertion, however, is contrary to the references cited herein that clearly provide the skilled artisan with information sufficient to allow the artisan to succeed in producing variants of SEQ ID NO: 2 that bind to an anti-*Ehrlichia* antibody. Sensitivity to substitutions is in large part based on upset of the packing of tertiary and quaternary structure present in most full size proteins. See, e.g., Bowie, page 1307. Branden & Tooze, Introduction to Protein Structure, Garland Publishing 1991 (copy of pages 12, 15 are attached) teach that the average length of helix is 10 amino acids, and a single strand of beta sheet is 7 amino acids. Thus, one of skill in the art would expect that tertiary structure is minimal in short sequences This is especially relevant for the about 20 amino acid sequences of the invention, because tertiary structure is minimal to nonexistent and quaternary structure is nonexistent. Consequently, concerns about disruption of function by amino acid substitution, for example, through disruption of amino acid packing at the core of a folded protein are minimized for the about 20 amino acid polypeptides of the invention.

Still further, those of skill in the art would know that, as Bowie observed in 1990, "An amino acid sequence encodes a message that determines the shape and function of a protein. This message is highly degenerate in that many different sequences can code for proteins with essentially the same structure and activity." Bowie, *et al.* p. 1306. Thus, contrary to the assertions of the Office Action, the practitioner would expect that substitutions could be made to

the polypeptide sequence with a reasonable expectation of success, *i.e.,* that the resulting sequence binds to anti-*Ehrlichia* antibodies.

Furthermore, making and testing the polypeptides and variants of the invention are trivial as outlined in the specification at, *inter alia*, page 10, line 6 through page 11, line 6; page 11, line 21 through page 16, line 8; Example 1, page 17, line 11 through page 19, line 13. Thus, it is trivial and routine to screen for the substitutions possible while maintaining 85% or greater identity and maintaining binding to anti-*Ehrlichia* antibodies according to the specification and there is a reasonable expectation of success in so doing. The test for enablement is not merely quantitative, since a considerable amount of experimentation is permissible, if it merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. The testing necessary to identify the claimed variants it is merely routine and the specification provides a reasonable amount of guidance to identify, make, and use the claimed variants.

As a whole, one of skill in the art would know how to make and use polypeptides consisting essentially of the about 20 amino acid polypeptide of SEQ ID NO:2 or phenotypically silent or conservative amino acid substitution variants of SEQ ID NO:2 that specifically bind to an anti-*Ehrlichia* antibody. Thus, the specification is enabled for the full scope of the claims and therefore meets the enablement requirement of 35 U.S.C. § 112, first paragraph. Consequently, Applicants respectfully request withdrawal of the rejection.

Rejection of Claims 1-9 Under 35 U.S.C. §102(a)

Claims 1-9 stand rejected under 35 U.S.C. §102(a) as allegedly anticipated by Waner *et al.* Applicants respectfully traverse.

Anticipation under 35 U.S.C. §102 requires the presence in a single prior art disclosure of each and every element of a claimed invention. *Lewmar Marine Inc. v. Barient Inc.,* 3 U.S.P.Q.2d 1766, 1767 (Fed. Cir. 1987).

The claims recite compositions of matter and articles of manufacture that consist essentially of an isolated polypeptide shown in SEQ ID NO:2, a phenotypically silent amino acid substitution variant of SEQ ID NO:2, and a conservative amino acid substitution variant of SEQ ID NO:2.

The Office asserts that there is nothing on the record to show that the claimed compositions are different from the prior art. See Office Action mailed Jan. 24, 2003, page 9. Applicants have clearly stated that the prior art does not teach or suggest the use of polypeptide fragments of about 20 amino acids as shown in SEQ ID NO:2. The Office has not alleged that the prior art teaches or suggests compositions containing such polypeptide fragments. The Office has not alleged that the prior art inherently teaches or suggest compositions containing polypeptide fragments of about 20 amino acids as shown in SEQ ID NO:2. Applicants respectfully request that the Office point to a specific portion of the reference that teaches the claimed polypeptide fragments or clearly state why such polypeptide fragments would be inherently present in the reference

The Office asserts that Waner teaches a commercial ELISA for *E. canis* and that the polypeptides recited in the instant invention would be inherent in the teachings of Waner. The Office is relying on an inherency theory to sustain this anticipation rejection. However, where an Examiner relies upon an inherency theory:

> the Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art. See *Ex parte Levy*, 17 U.S.P.Q. 1461,1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original); M.P.E.P. §2112.

The Office has not provided a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art. Waner does not teach or suggest SEQ ID NO:2 or variants thereof. No where in Waner is the polypeptide sequence NTTTGVFGLKQDWDGATIKD (SEQ ID NO:2) or variants thereof. Waner teaches the use of whole proteins or whole cells as antigens, and does not teach or suggest the use of polypeptide fragments. The burden is on the Office to show that the alleged prior art teaches the claimed subject matter. The Office has provided no reasoning or evidence tending to show inherency in the instant case. The Office has not provided any reasoning or evidence why the claimed polypeptide fragments would be present in Waner.

Furthermore, the Office Action has provided no extrinsic evidence, other than a bald assertion, to support the alleged inherency finding.

> To establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." Inherency, however, **may not be established by probabilities or possibilities**. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. *See In re Robertson*, 49 U.S.P.Q.2d 1949, 1950-1951 (Fed. Cir. 1999) (citations omitted)(emphasis added); M.P.E.P §2112.

The Office Action has provided no extrinsic evidence that the claimed polypeptide fragments are present in the cited reference.

The Office additionally states:

> The Examiner disagrees with Applicant's assertion that the *E. canis* antigen of the prior art is not apart from the infected cells, since Waner et al teach [the] antigen was derived from the mouse J774.A1-infected cells. See Office Action mailed Jan. 24, 2003, page 9, last full paragraph.

Applicants have not asserted that Waner's antigens are not apart from infected cells. Applicants have clearly stated that Waner teaches **entire cells OR whole proteins** as assay antigens. See Response dated Nov. 4, 2002, page 23, first full paragraph. The Office has not addressed the fact that the claims are drawn to compositions of matter and articles of manufacture that consist essentially of an isolated polypeptide shown in SEQ ID NO:2, and that Waner only teaches the use of entire cells or whole proteins as assay antigens. The Office has provided no reasoning or evidence that Waner teaches a distinct polypeptide fragment shown in SEQ ID NO:2 or the specified variants thereof.

The Office has not pointed to any teaching or suggestion in Waner of distinct *E. canis* polypeptide fragments as shown in SEQ ID NO:2. Instead, Waner teaches an IFA for *Ehrlichia canis* that uses DH82 cells that are heavily infected with *E. canis* as an antigen. See page 240, second column, last paragraph. Waner also teaches an ELISA for *E. canis* that uses an *E. canis* antigen derived from mouse J774.A1-infected cells. See page 241, first column, first full paragraph. Waner, therefore, teaches entire cells or whole proteins as assay antigens. As such, Waner can not teach, suggest, or inherently disclose the specific, individual polypeptides shown in SEQ ID NO:2 or the specified variants of SEQ ID NO:2. There is no teaching in Waner, directly or inherently, that would direct one of skill in the art to the particular defined sequences of SEQ ID NO:2 or the specified variants for any reason. Waner does not teach or suggest that polypeptides of SEQ ID NO:2 would be useful as individual polypeptides apart from entire *E. canis* infected cells or entire proteins. Waner provides no recognition or suggestion of the distinct polypeptides shown in SEQ ID NO:2 or the specified variants or any other *E. canis* polypeptide fragments.

Importantly, the instant specification teaches that:

> Indirect immunofluorescense assays (IFA) and enzyme-linked immunosorbent assays (ELISA) are frequently used as aids in the diagnosis of these diseases. These assays measure or otherwise detect the binding of anti-*Ehrlichia* antibodies from a patient's blood, plasma, or serum to infected cells, cell lysates, or purified *Ehrlichia* proteins. However, currently known assays for detecting anti-*Ehrlichia* antibodies or fragments thereof are severely limited in usefulness because of sensitivity and specificity issues directly related to the impure nature of the *Ehrlichia* antigen used in these tests. See page 2, line 21 through page 3, line 2 (emphasis added).

The instant invention provides highly purified reagents for the detection *Ehrlichia*, that is, polypeptides of about 20 amino acids, whereas Waner teaches the use of reagents comprising whole infected cells or whole *E. canis* proteins derived from infected cells. The Waner reagents are impure reagents, which the instant specification teaches are of limited usefulness due to the sensitivity and specificity issues. For instance, Example 1 demonstrates that assays that use synthetic peptides were more sensitive and specific than assays that use native *E. canis* antigens, i.e., partially purified *E. canis* antigens.

Further, the Office asserts:

> Since the claimed invention encompass variants of SEQ ID NO:2, one skilled in the art could reasonably conclude that the *E. canis* polypeptide of the prior art is a variant of SEQ ID NO:2 since, Applicant has provided no side-by-side comparison to show that the claimed polypeptide differs from the *E. canis* polypeptide of the prior art. See Office Action mailed Jan. 24, 2003, page 10.

However, the instant specification at, *inter alia*, page 19, line 17 through page 21, line 6, and Table 2, indicates that unlike the whole protein-based or whole cell-based assays of Waner, the embodiments of the present invention enable unexpectedly sensitive and selective testing for *E. canis* antibody, more sensitive and selective than either the alleged "gold standard" of IFA (see Waner, abstract) or the ELISA assay of Waner. For example, the Waner ELISA assay was

about 16% less sensitive than IFA at seven days post infection (4/6 positives versus 5/6 positives) but finished approximately equivalent to the IFA assay. See Waner, page 242, left column, first full paragraph. In contrast, utilizing the polypeptides contemplated in the present invention, five true negatives were correctly identified as such where the same samples were falsely identified as positive by IFA. See, e.g., Table 2. Further, seven true positives identified as such utilizing the polypeptides contemplated in the present invention were falsely identified as negative by IFA. See, e.g., Table 2. Fifty-seven true positives were properly identified by both assays. Thus, the embodiments of the present invention allow for greater sensitivity and selectivity for *E. canis* antibodies than the assays presented by Waner. Therefore, in a side-by-side comparison, the polypeptides of the instant invention provided assays with greater selectivity and sensitivity than the ELISA and IFA assays of Waner.

The Office further asserts:

> The Examiner also disagrees with Applicant's assertion that Waner et al do not identify the polypeptide fragments for diagnostic use nor do Waner et al teach or suggest that the polypeptides of SEQ ID NO:2. There is no requirement or limitation in the claims that the composition and article of manufacture be used for diagnostic purposes. See Office Action mailed Jan. 24, 2003, page 10

The question presented is whether Waner teaches or suggests the claimed polypeptide fragments and not whether Waner teaches or suggests their diagnostic use. The claims are drawn to compositions, not to methods of use of the compositions. As such, the lack of a diagnostic use limitation in the claims is of no importance.

Waner does not anticipate claims 1-9 because Waner does not teach, suggest, or inherently disclose each and every element of claims 1-9. Thus, Applicants respectfully request withdrawal of the rejection.

Rejection of Claims 1-9 Under 35 U.S.C. §102(b)

Claims 1-9 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by Cadman *et al.* The Office Action asserts that the polypeptide compositions and article of manufacture of the invention are inherently present in the assays disclosed in Cadman. Applicants respectfully traverse.

The Office asserts that "there is nothing on the record to show that the claimed composition and article of manufacture differs [from] the composition and article of manufacture of the prior art." See Office Action mailed Jan. 24, 2003, page 12. Applicants have clearly stated that the prior art does not teach or suggest the use of polypeptide fragments of about 20 amino acids as shown in SEQ ID NO:2. The Office has not alleged that the prior art teaches or suggests compositions containing such polypeptide fragments. The Office has not alleged that the prior art inherently teaches or suggest compositions containing polypeptide fragments of about 20 amino acids as shown in SEQ ID NO:2. Applicants respectfully request that the Office point to a specific portion of the reference that teaches the claimed polypeptide fragments or clearly state why such polypeptide fragments would be inherently present in the reference.

The Office appears to be relying on an inherency theory to sustain this anticipation rejection. Where an Examiner relies upon an inherency theory:

> the Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art. See *Ex parte Levy*, 17 U.S.P.Q. 1461,1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original); M.P.E.P. §2112.

The Office has not provided a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art. Cadman does not teach or suggest SEQ ID NO:2 or variants thereof. No

where in Cadman is the polypeptide sequence NTTTGVFGLKQDWDGATIKD (SEQ ID NO:2) or variants thereof. Cadman teaches the use of whole proteins or whole cells as antigens, and does not teach or suggest the use of polypeptide fragments. The burden is on the Office to show that the alleged prior art teaches the claimed subject matter. The Office has provided no reasoning or evidence tending to show inherency in the instant case. The Office has not provided any reasoning or evidence why the claimed polypeptide fragments would be present in Cadman.

Furthermore, the Office Action has provided no extrinsic evidence, other than a bald assertion, to support the alleged inherency finding.

> To establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." Inherency, however, **may not be established by probabilities or possibilities**. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. *See In re Robertson*, 49 U.S.P.Q.2d 1949, 1950-1951 (Fed. Cir. 1999) (citations omitted)(emphasis added); M.P.E.P §2112.

The Office Action has provided no extrinsic evidence that the claimed polypeptide fragments are present in the cited reference.

The Office additionally states:

> Cadman et al teach nitrocellulose paper containing *E. canis* antigen, therefore the prior art teaches polypeptides that are apart from whole cells. See Office Action mailed Jan. 24, 2003, page 12.

Applicants have not asserted that Cadman's antigens are not apart from infected cells. Applicants have clearly stated that Cadman teaches **entire cells OR whole proteins** as assay antigens. See Response dated Nov. 4, 2002, page 26, first full paragraph. The Office has not addressed the fact that the claims are drawn to compositions of matter and articles of manufacture that consist essentially of an isolated polypeptide shown in SEQ ID NO:2, and that

Cadman only teaches the use of entire cells or whole proteins as assay antigens. The Office has provided no reasoning or evidence that Cadman teaches a distinct polypeptide fragment shown in SEQ ID NO:2 or the specified variants thereof.

The Office has not pointed to any teaching or suggestion in Cadman of distinct *E. canis* polypeptide fragments as shown in SEQ ID NO:2. and the claimed variants. Cadman teaches an IFA for *Ehrlichia canis* that uses DH82 cells that are heavily infected with *E. canis* as an antigen. See Cadman, first column, fourth paragraph. Cadman also teaches a dot-blot enzyme linked immunoassay (DBELIA) for *E. canis* that uses an *E. canis* antigen purified from infected DH82 cells. See Cadman, first column, fifth paragraph. As such, Cadman teaches the use of whole *E. canis* infected cells or whole proteins purified from *E. canis* infected cells in the disclosed assays. Cadman does not teach, suggest, or inherently disclose that any specific polypeptide fragments are of any particular use, nor does it teach, suggest, or disclose the claimed polypeptide fragments.

- Importantly, the instant specification teaches that:

> Indirect immunofluorescense assays (IFA) and enzyme-linked immunosorbent assays (ELISA) are frequently used as aids in the diagnosis of these diseases. These assays measure or otherwise detect the binding of anti-*Ehrlichia* antibodies from a patient's blood, plasma, or serum to infected cells, cell lysates, or purified *Ehrlichia* proteins. However, currently known assays for detecting anti-*Ehrlichia* antibodies or fragments thereof are severely limited in usefulness because of sensitivity and specificity issues directly related to the impure nature of the *Ehrlichia* antigen used in these tests. See page 2, line 21 through page 3, line 2 (emphasis added).

The instant invention provides highly purified reagents for the detection *Ehrlichia*, that is, polypeptides of about 20 amino acids, whereas Cadman teaches the use of reagents comprising whole infected cells or whole *E. canis* proteins derived from infected cells. The Cadman

reagents are impure reagents, which the instant specification teaches are of limited usefulness due to the sensitivity and specificity issues. For instance, Example 1 demonstrates that assays that use synthetic peptides were more sensitive and specific than assays that use native *E. canis* antigens, i.e., partially purified *E. canis* antigens.

Further, the Office asserts:

> Since the claimed invention encompass variants of SEQ ID NO:2, therefore one skilled in the art could reasonably conclude that the *E. canis* polypeptide of the prior [art] is a variant of SEQ ID NO:2 since, Applicant has provided no side-by-side comparison to show that the claimed polypeptide differs from the E. canis polypeptide of the prior art. See Office Action mailed Jan. 24, 2003, page 12.

However, the instant specification at, *inter alia*, page 19, line 17 through page 21, line 6, and Table 2, indicates that unlike the whole protein-based or whole cell-based assays of Cadman, the embodiments of the present invention enable unexpectedly sensitive and selective testing for *E. canis* antibody, more sensitive and selective than either the alleged "gold standard" of IFA. Furthermore, as presented above, the results, *inter alia*, page 19, line 17 through page 21, line 6, and Table 2, indicate that unlike the whole protein-based assays of Cadman, the embodiments of the present invention enable unexpectedly sensitive and selective testing for *E. canis* antibody, more sensitive and selective than either IFA or the DBELIA assay of Cadman. For example, the Cadman DBELIA assay was only about 92% as sensitive and 96% as specific as IFA. As explained above, the polypeptides of the present invention provide results superior to the "gold standard" IFA. *See* Cadman, page 362, paragraph bridging the columns. For example, utilizing the peptides contemplated in the present invention, 5 true negatives were identified as such where the same samples were falsely identified as positive by IFA. Further, 7 true positives identified as such utilizing the peptides contemplated in the present invention were falsely identified as negative by IFA. Fifty-seven true positives were properly identified by both assays.

Thus, the embodiments of the present invention allow unexpectedly sensitive and selective assays for *E. canis* antibody, which are not anticipated by the teachings of Cadman. Therefore, in a side-by-side comparison, the polypeptides of the instant invention provided assays with greater selectivity and sensitivity than the assays of Cadman.

The Office further asserts:

> The Examiner also disagrees with Applicant's assertion that Cadman et al do not identify the polypeptide fragments for diagnostic use nor do Cadman et al teach or suggest that the polypeptides of SEQ ID NO:2. There is no requirement or limitation in the claims that the composition and article of manufacture be used for diagnostic purposes. See Office Action mailed Jan. 24, 2003, page 12.

The question presented is whether Cadman teaches or suggests the claimed polypeptide fragments and not whether Cadman teaches or suggests their diagnostic use. The claims are drawn to compositions, not to methods of use of the compositions. As such, the lack of a diagnostic use limitation in the claims is of no importance.

Cadman does not teach each and every element of the claimed invention. Further, Cadman does not teach, suggest or inherently disclose the unexpectedly enhanced function afforded by the polypeptide fragments contemplated in the present invention. Therefore, Cadman does not anticipate the claimed invention. Applicants respectfully request withdrawal of the rejection.

Rejection of Claims 1-9 Under 35 U.S.C. §102(b)

Claims 1-9 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by Rikihisa et al. (WO 99/13720). Applicants respectfully traverse.

The Office asserts that Rikihisa teaches the polypeptide of SEQ ID NO:2, and that an article of manufacture is inherent in the teachings of Rikihisa. However, Rikihisa does not teach

or suggest the use of polypeptides consisting essentially of the about 20 amino acid polypeptide of SEQ ID NO:2 or phenotypically silent or conservative amino acid substitution variants of SEQ ID NO:2 that specifically bind to an anti-*Ehrlichia* antibody. Rather, Rikihisa relates to a complete 288 amino acid protein sequence, that is, a full length protein. The instant claims, however, recite a polypeptide fragment of about 20 amino acids. The instant specification teaches that use of these polypeptides fragments provide a sensitivity and selectivity advantage over the use of whole proteins. See e.g., specification page 2, line 21 through page 3, line 2 (teaching that assays using purified *Ehrlichia* proteins (i.e., whole *Ehrlichia* proteins) are limited in usefulness due to sensitivity and specificity issues directly related to the impure nature of the *Ehrlichia* antigen used in these tests. See page 2, line 21 through page 3, line 2). Thus, contrary to the Office's assertions, there is evidence that the claimed composition and article of manufacture differs from Rikihisa.

Furthermore, there is no teaching in Rikihisa, directly or inherently, that would *direct* one of skill in the art *to* the particular polypeptide fragments of the invention. Rikihisa does not teach or suggest that polypeptides of the instant invention would be useful as individual polypeptides apart from the entire *E. canis* P30 protein. More importantly, Rikihisa provides no teaching or suggestion that polypeptides of the invention would enable unexpectedly sensitive and selective testing for *E. canis* antibody, significantly more sensitive and selective than even IFAs known in the art.

The Office further asserts:

> The Examiner disagrees with Applicant's assertion that Rikihisa et al does not identify the polypeptide fragments for diagnostic use nor do Rikihisa et al teach or suggest that the polypeptides of SEQ ID NO:2. There is no requirement or limitation in the claims that the composition and article of manufacture be used for diagnostic purposes. See Office Action mailed Jan. 24, 2003, page 14.

The question presented is whether Rikihisa teaches or suggests the claimed polypeptide fragments and not whether Rikihisa teaches or suggests their diagnostic use. The claims are drawn to compositions, not to methods of use of the compositions. As such, the lack of a diagnostic use limitation in the claims is of no importance.

Rikihisa does not teach each and every element of the claimed invention and it does not teach, suggest or inherently disclose the unexpectedly enhanced function afforded by the **polypeptide fragments** of the present invention. Therefore, Rikihisa does not anticipate the claimed invention. Applicants respectfully request withdrawal of the rejection.

Conclusion

Applicants respectfully submit that the claims are in a condition for allowance. If the Examiner of the opinion that that a telephone conference would expedite the prosecution of the application, the Examiner is encouraged to contact Applicants undersigned representative.

Respectfully submitted,

Date: 6/24/03 by: _____

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